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Discussion

Dr. B. B. Newbould. What proportion of severe gastrointestinal side-effects, such as ulcers, can be attributed to local concentrations of anti-inflammatory analgesic drugs, and what proportion to systemic levels? In view of the fact that many analgesic anti-inflammatory agents can cause damage to the gastrointestinal tract of animals following parenteral administration, can different methods of presentation really reduce the incidence of side-effects in man or can the lower incidence of side-effects following, for example, the administration of enteric coated tablets, be attributed to more erratic absorption? Have any observations been made on the gastrointestinal irritant effects of aspirin in patients taking cytotoxic drugs? If Dr. Croft's hypothesis on cellular proliferation is correct then aspirin should have severe effects on the gastrointestinal tract of patients receiving therapy with cytotoxic drugs.

Dr. A. J. Hale. Mitotic counts of cellular turnover rate can be extremely misleading. For example, an apparent increased cell turnover rate can be caused by arresting cells in mitosis; quite a number of agents

will cause this, so a high number of mitosing cells among non-mitosing cells may in fact refer to arrest. If there is a larger amount of DNA in the gastric washings, and the amount is not greater than twofold, this would support the idea that there was an arrest of cells in mitosis because a cell in mitosis has twice the amount of DNA than has the normal non-dividing cell, so that it would be expected that the DNA content would go up. Therefore, to argue that there is increased cell turnover from an increased mitotic count and from a limited increased amount of DNA is a dangerous thing to do.

Dr. D. G. Davey. I think Dr. Croft's paper should possibly have been called "The Action of Anti-inflammatory Substances on the Gastric Mucosa". Of the four substances he has been concerned with, probably only paracetamol is purely analgesic in action. Aspirin has analgesic and anti-inflammatory properties, phenylbutazone is similar, but I doubt if indomethacin has any analgesic action, although it is certainly anti-inflammatory. Of the four substances, then, it appears that only the pure analgesic, that is, paracetamol, was without action on the gastric mucosa.

Dr. Prescott in his talk mentioned a paper by Brodie and his colleagues (1965), concerned with the effects of, amongst other substances, indomethacin, aspirin, and phenylbutazone on the protein-binding of corticosteroids, and all appear to cause a release of corticosteroids. It is also known, as indicated by Dr. Prescott, that the corticosteroids parallel the other anti-inflammatory agents in their effect on the gastric mucosa. Would it not seem to Dr. Croft that the action of these substances on the alimentary canal, and possibly the particular action described by him, is correlated in some way with their anti-inflammatory action, and is not a simple irritant effect.

Dr. D. N. Croft. To put this in perspective, Hollander's remarks in 1946 should be stated, namely that exfoliation is a physiological response to mild irritants, and there are many substances and physical phenomena which will produce this natural physiological response of the gastric mucosa. As far as the local aspirin-like irritant effects of drugs is concerned, apart from the references I have already given, I know of no conclusive data about the proportion of patients taking drugs who develop clinical side-effects. The present formulations of soluble aspirin dissolve very rapidly, and the local effect of the macroscopic particles is not in my opinion of primary importance. The comparison of occult bleeding with major bleeding has probably led to confusion as there are other factors involved in the pathogenesis of severe bleeding. These need to be investigated. There is evidence that cytotoxic drugs reduce the mitosis rate in gut epithelium, and this may lead to an histological abnormality. It would be interesting to see if these drugs affect aspirin-induced bleeding. High mitosis counts do not prove a high turnover, and this is why we measured the rate of loss of cells in addition to the mitosis counts. In the steady state the rate of loss of cells must be in equilibrium with their production, and our data indicated that there was a higher rate of loss of cells per unit area in patients with atrophic gastritis

compared to normal. We think that the data on mitosis counts and gastric DNA rate taken together point to a high turnover in this condition. There is a 2½-fold increase in the amount of gastric DNA within 5 min of giving aspirin. This is too short a time for aspirin to have an effect on mitosis of the cell, and I think it is an irritant phenomenon.

Dr. M. J. S. Langman. Dr. Croft's evidence seems to suggest that atrophic gastritis may protect against occult bleeding. We have evidence that when erosions occur that are associated with severe bleeding they almost always appear in atrophic mucosa. We have examined gastric mucosal biopsies from people who had had aspirin bleeding and others bleeding without previous aspirin intake, and we have seen no convincing difference in the overall picture, although the erosions, in general, appeared in the atrophic mucosa. Although it seems that occult bleeding is protected against in atrophic mucosa, I am not certain that this is true in overt bleeding: indeed, the reverse may be the case.

Dr. D. N. Croft. Release of cortisone has been considered for some time as one of the methods for this response of the stomach to anti-inflammatory substances. I do not think this is the main factor. It may well be that patients with atrophic gastritis may be more prone to severe or overt bleeding.

Mr. A. W. Lessin. Is there any evidence of mucosal cells taking up aspirin, and is this possibly the reason why they come off in greater numbers? Have you looked for aspirin within the mucosal cells?

Dr. B. K. Martin. Exfoliation of cells takes place in the stomach and in the urinary tubules. I believe there is a common feature here. The kidney re-capitulates in miniature some of the processes taking place in the stomach, for re-absorption of drug occurs in the renal tubules. In both tissues the absorption of drug takes place from an acidic environment into a more or less neutral environment. Elsewhere I have advanced theoretical considerations* suggesting that the absorption of an acidic drug, from an acidic environment into a neutral environment, may well give rise to an accumulation of drug anions in the mucosal cells. It should be emphasised, however, that this will relate only to the first layer of cells. Both the gastric mucosal cells and the renal tubular cells are therefore involved in a process of drug absorption, and both may attain relatively high drug concentrations.

Dr. D. N. Croft. We have not measured aspirin in the cells, although this has been suggested by Professor Milne. It is perhaps at these two sites, stomach and kidney, that aspirin is most concentrated, the stomach because the drug remains there for a variable period during absorption and the kidney because it is being concentrated there in the process of excretion. Perhaps it is this factor of local concentration which explains why these are the sites where effects are produced.

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